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ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/655,540	CARTER ET AL.	
	Examiner	Art Unit	
	Russell S. Negin	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 April 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26,30 and 31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-26,30 and 31* is/are rejected.

7)☒ Claim(s) *1* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Comments

The finality of this application has been withdrawn as indicated in the interview summary mailed 11 May 2007. This action is in response to a request for reconsideration and an amended set of claims filed by applicant on 27 April 2007.

The amendment filed by applicant has been entered.

Claims 1-26 and 30-31 are pending and examined in this Office action.

Specification

The objection to the specification in the amendment filed 20 December 2006 under 35 U.S.C. 132(a) because it introduces new matter into the disclosure is withdrawn due to amendments made to the specification in the reply of applicants on 27 April 2007.

Claim Objections

The objections to claims 1-26, 30-31, and 34-38 because of informalities in the set of claims filed 20 December 2006 are withdrawn due to amendments made to the set of claims filed on 27 April 2007.

The following objection is newly applied:

Claim 1 is objected to because of the following informalities:

There is a period following the status identifier "(Currently Amended)" on line 1 of this claim.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-13, 17-18, 21-22, and 30-31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1, on lines 14-15, indicates "relative ratios" where it is indefinite as to the specific type of ratio being examined (i.e. concentration, volume, or weight). Furthermore, a ratio is the relationship between two of more things, usually expressed as a quotient. In the instant case, it is unclear as to between what two or more agents the ratio is.

Claim 1 has the phrase on line 19-20 stating, "algebraic manipulations relating full and reduced ray mixture models," where it is unclear as to how the mixture models are to be related.

Claim 2 recites "[t]he method of claim 1 wherein said method is applied to a plurality of full-ray groups." The phrase "said method" lacks clear antecedent basis because there are at least two types of "methods" referenced in claim 1, the "method of detecting an interaction among agents" as recited in line 1, and the "statistical methods"

recited in step (f). It is thus unclear as to which method it is referred to by the phrase "said method" in claim 2.

Claim 6, on lines 10-11, indicates "relative ratios" where it is indefinite as to the specific type of ratio being examined (i.e. concentration, volume, or weight). Furthermore, a ratio is the relationship between two of more things, usually expressed as a quotient. In the instant case, it is unclear as to between what two or more agents the ratio is.

Claim 6 has the phrase on lines 15-16 stating, "algebraic manipulations relating full and reduced ray mixture models," where it is unclear as to how the mixture models are to be related.

Claim 7 recites "[t]he method of claim 6 wherein said method is applied to a plurality of full-ray groups." The phrase "said method" lacks clear antecedent basis because there are at least two types of "methods" referenced in claim 6, the "method of detecting an interaction among agents" as recited in line 1, and the "statistical methods" recited in step (e). It is thus unclear as to which method it is referred to by the phrase "said method" in claim 7.

Claim 21 has the phrase on lines 7-8 stating, "algebraic manipulations relating full and reduced ray mixture models," where it is unclear as to how the mixture models are to be related.

Claim 30, on line 14, indicates "relative ratios" where it is indefinite as to the specific type of ratio being examined (i.e. concentration, volume, or weight). Furthermore, a ratio is the relationship between two of more things, usually expressed

as a quotient. In the instant case, it is unclear as to between what two or more agents the ratio is.

Claim 30 has the phrase on lines 19-20 stating, "algebraic manipulations relating full and reduced ray mixture models," where it is unclear as to how the mixture models are to be related.

Claim 31, on lines 11-12, indicates "relative ratios" where it is indefinite as to the specific type of ratio being examined (i.e. concentration, volume, or weight). Furthermore, a ratio is the relationship between two of more things, usually expressed as a quotient. In the instant case, it is unclear as to between what two or more agents the ratio is.

Claim 31 has the phrase on lines 16-17 stating, "algebraic manipulations relating full and reduced ray mixture models," where it is unclear as to how the mixture models are to be related.

Claim Rejections - 35 USC § 101

The rejections of claims 1-12, 14-26, and 30-31 under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter is withdrawn due to amendments made by applicant to the set of claims filed on 27 April 2007.

Claim Rejections - 35 USC § 102

The rejection of claims 1-5, 14-22, 34, and 36 under 35 U.S.C. 102(b) as being anticipated by Gennings et al. [Journal of Agricultural, Biological, and Environmental Statistics, volume 3, pages 1-16, 1998] is withdrawn due to arguments made by applicant on pages 12-14 of the Remarks of 27 April 2007.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 14 is rejected under 35 U.S.C. 102(b) as being anticipated by Gennings et al. [Journal of Agricultural, Biological, and Environmental Statistics, volume 2, 1997, pages 198-211].

Claim 14 is drawn to a method of determining an interaction threshold between agents in a group or mixture comprising generating a model that permits estimation of the boundaries between a region of additivity and a region of interaction of said agents wherein said generation is carried out in order to detect, characterize or predict an outcome caused by exposure to said agents in said group or mixture.

The article of Gennings et al. (1997), entitled, "Detection of departures from additivity in mixtures of many chemicals with a threshold model," states on the last seven lines of page 199:

> Suppose that we are interested in studying the interaction among c chemicals in combination, where dose-response information is available on each single chemical. Assume that the existence of a threshold is reasonable for these chemicals. Further, suppose that we are particularly interested in the effect associated with certain combinations of these chemicals. We propose to construct a threshold additivity model that can be used to predict a response at each combination of interest. The observed response at these combination points can then be compared to that predicted under the assumption of additivity.

Consequently, Gennings et al. (1997) teaches a threshold additivity model for the purpose of analyzing groups or mixtures.

Such a threshold additivity model is displayed quantitatively as equation 1.1 on page 201 of Gennings et al. (1997). The top "branch" of equation 1.1 indicates an additivity model. Above a certain threshold, δ, the generation of a region containing a departure from additivity from the elements of the group (i.e. a region of interaction) is witnessed. The results are plotted in Figures such as Figure 1 of Gennings et al. (1997).

Claim Rejections - 35 USC § 103

The rejections of claims 6-14, 23-26, and 35 under 35 U.S.C. 103(a) as being unpatentable over Gennings et al. (1998) are withdrawn due to arguments made by the applicant on pages 14-15 of the Remarks of 27 April 2007.

The rejections of claims 30-31 and 37-38 under 35 U.S.C. 103(a) as being unpatentable over Gennings et al. (1998), in further view of Schork et al. [US PGPUB 2002/0077775] are withdrawn due to arguments made by the applicant on pages 15-16 of the Remarks of 27 April 2007.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The following rejections are newly applied:

Claims 1-26 and 30-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gennings et al. [Journal of Agricultural, Biological, and Environmental Statistics, volume 3, pages 1-16, 1998] in view of Gennings et al. [Journal of Agricultural, Biological, and Environmental Statistics, volume 2, 1997, pages 198-211]. The first reference is referred to in this Office action as Gennings et al. (1998); the second reference is referred to in this Office action as Gennings et al. (1997).

In light of the indefiniteness of the claims as set forth above, the art is being applied to the best interpretation of the claims as currently written.

Claim 1 is drawn to a method of detecting interactions among agents in a group or mixture comprising seven steps.

The preamble of claim 1 indicates a method of detecting an interaction among agents in a group or mixture using fixed-ratio ray design and determining whether subsets of said agents also interact. The first step of instant claim 1 recites determining an additivity model from single dose-response data. The second step of instant claim 1 recites fitting a mixture model in terms of total dose to mixture-dose response data from fixed-ratio rays for said agents in said group or mixture. The third step of instant claim 1 recites comparing the additivity and mixture models. The fourth and fifth steps of instant claim 1 recite removing a subset of agents from the group or mixture and repeating this step for multiple subsets, respectively. The sixth step of instant claim 1 recites determining the interaction of agents by utilizing the statistical methods based on the results of the fourth and fifth steps of the method. The seventh step of claim 1 provides the results in the form of a plot or table.

The study of Gennings et al. (1998), entitled, "Combination threshold models with design optimization along fixed-ratio rays," states in the abstract:

> Threshold models are useful in concentration-effect studies to describe regions of exposure that result in background response. These models are parameterized to estimate the background response, the concentration-effect relationship, and the join-point between the two, called the threshold. If the threshold is different than zero, then it can be inferred that exposure to the chemical at regions below the threshold do not increase risk above background. When the exposure is to many chemicals, fixed-ratio ray designs can be used to assess risk to single chemicals and to specified mixtures of chemicals. This article describes the inference resulting from use of a threshold model for correlated binary data supported by a ray design. An example of the effect of three hepatotoxins in the development of rats is provided. In addition, a two-stage simultaneous optimal design criterion is described for the threshold model along rays of fixed ratios. The approach is illustrated through a simulation study of the hepatotoxin data.

Consequently, Gennings et al. (1998) teaches usage of mixtures and analysis (using fixed ratio rays) of mixture data in rats (test subjects).

The first step of instant claim 1 recites determining an additivity model from single dose-response data. Gennings et al. (1998) teaches the use of an additivity model in section 2.2 on page 4, entitled, "Estimation of an additivity threshold surface." The first equation in section 2.2 of Gennings et al. (1998) teaches such an additivity model quantitatively.

The second step of instant claim 1 recites fitting a mixture model in terms of total dose to mixture-dose response data from fixed-ratio rays for said agents in said group or mixture. The third step of instant claim 1 recites comparing the additivity and mixture models. A threshold mixture model is taught through section 2 on page 3 of Gennings et al. (1998), entitled, "Threshold model for proportional data," and section 2.1 on pages 3-4 of Gennings et al. (1998), entitled, "Simultaneous estimation along each ray using a threshold model." Section 2.3.2 on pages 5-6 of Gennings et al. (1998), entitled, "Comparison of predicted thresholds along each mixture ray to the location of the threshold under additivity," compares the additive and mixture models by using thresholds.

The fourth and fifth steps of instant claim 1 recite removing a subset of agents from the group or mixture and repeating this step for multiple subsets, respectively. The sixth step of instant claim 1 recites determining the interaction of agents by utilizing the statistical methods based on the results of the fourth and fifth steps of the method. In the example study in section 4 of Gennings et al. (1998) on pages 8-12 of Gennings et al. (1998), Table 4 of Gennings et al. (1998) on page 11 illustrates modeling the interaction of three agents (DEHP, HEPT, and TCE) by removing two of the three

agents, and then examining the effects of a mixture on the mixture in Ray 4, which is a 70:1:29 mixture of DEHP, HEPT, and TCE, respectively. Table 3-5 on page 11-12 of Gennings et al. (1998) tabulate a plurality of full-ray groups. Figure 2 on page 10 if Gennings et al. (1998) is interpreted as a comparison between an additivity model and a mixture model.

However, Gennings et al. (1998) fails to teach that when the subsets of two agents are removed, the remaining agents (plural) must maintain their relative ratios (i.e. fourth step of instant claim 1).

Gennings et al. (1997) teaches such a phenomenon in their study, entitled "Detection of departures from additivity in mixtures of many chemicals with a threshold model." Specifically, in comparing the plots Figures 1a and 1b on page 200 of Gennings et al. (1997), a subset of chemicals are removed and a subset of chemical remain. As is stated in the Figure caption:

> Figure 1. Three-dimensional representation of a threshold additivity surface between four chemicals over dose ranges of Chemical 1 and Chemical 2 when: (a) Chemical 3 and Chemical 4 are not included in the mixture (= 0) and (b) Chemical 3 = 0.1 and Chemical 4 = 0.1.

Consequently, while in Figure 1B, all of the constituents are in the mixture, in Figure 1A of Gennings et al. (1997), the subset of chemicals 3 and 4 are removed, leaving chemicals 1 and 2.

The purpose of the study of Gennings et al. (1997) is stated in the introduction, which states, "The evaluation of risk associated with mixtures of chemicals is often needed when the number of chemicals in the mixture is large when the concentration of individual chemicals is low."

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the fixed ratio ray optimization study of Gennings et al. (1998) by use of the additivity models of Gennings et al. (1997) because while Gennings et al. (1998) measures fixed ratio rays in simple ternary systems, Gennings et al. (1997) uses analogous principles with the advantage of investigating additivity in more complex quaternary mixtures.

Claim 2 is dependent from claim 1 with the additional limitation of specifying a plurality of full ray groups. Table 4 of page 11 of Gennings et al. (1998) lists a plurality of full-ray groups.

Claim 3 is dependent from claim 1 with the additional limitation of carrying out the second and third steps of instant claim 1 for the subset of agents. Gennings et al. (1997) carries out such a process in Figure 1. Specifically, in comparing the plots Figures 1a and 1b on page 200 of Gennings et al. (1997), a subset of chemicals are removed and a subset of chemical remain. As is stated in the Figure caption:

> Figure 1. Three-dimensional representation of a threshold additivity surface between four chemicals over dose ranges of Chemical 1 and Chemical 2 when: (a) Chemical 3 and Chemical 4 are not included in the mixture (= 0) and (b) Chemical 3 = 0.1 and Chemical 4 = 0.1.

Consequently, while in Figure 1B, all of the constituents are in the mixture, in Figure 1A of Gennings et al. (1997), the subset of chemicals 3 and 4 are removed, leaving chemicals 1 and 2.

The purpose of the study of Gennings et al. (1997) is stated in the introduction, which states, "The evaluation of risk associated with mixtures of chemicals is often needed when the number of chemicals in the mixture is large when the concentration of individual chemicals is low."

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the fixed ratio ray optimization study of Gennings et al. (1998) by use of the additivity models of Gennings et al. (1997) because while Gennings et al. (1998) measures fixed ratio rays in simple ternary systems, Gennings et al. (1997) uses analogous principles with the advantage of investigating additivity in more complex quaternary mixtures.

Claim 4 is dependent from claim 1 with the extra limitation of showing an additivity curve compared with a mixture curve. Figure 2 of Gennings (1998) on page 10 illustrates a comparison of additivity (i.e. model predicted) and mixture model (i.e. observed) with the purpose of comparing the two types of statistical analyses.

Claim 5 is dependent from claim 1 with the additional limitation of determining simultaneous confidence bands on the difference between the additivity curve and the mixture curve.

Confidence bands are described in the full paragraph of page 10 of Gennings et al. (1998), which states:

> As evidenced by the data points in Figure 2 and the p values in Table 3, the proportion of prenatal loss across litters is large. The 95% confidence interval for the threshold for DEHP covers the entire experimental region ...[and] the threshold interval for total dose along the mixture ray.

Claim 6 is drawn to a method of detecting interactions among agents in a group or mixture comprising six steps.

The preamble of claim 6 indicates a method of detecting an interaction among agents in a group or mixture using fixed-ratio ray design and determining whether subsets of said agents also interact. The first step of instant claim 6 recites fitting a polynomial additivity to dose-response data. The second step of instant claim 6 is statistical analysis of higher order terms in the polynomial model. The third and fourth steps of instant claim 6 recite removing a subset of agents from the group or mixture and repeating this step for multiple subsets, respectively. The fifth step of instant claim 6 recites determining the interaction of agents by utilizing the statistical methods based on the results of the third and fourth steps of the method. The sixth step of claim 6 provides the results in the form of a plot or table.

The study of Gennings et al. (1998), entitled, "Combination threshold models with design optimization along fixed-ratio rays," states in the abstract:

> Threshold models are useful in concentration-effect studies to describe regions of exposure that result in background response. These models are parameterized to estimate the background response, the concentration-effect relationship, and the join-point between the two, called the threshold. If the threshold is different than zero, then it can be inferred that exposure to the chemical at regions below the threshold do not increase risk above background. When the exposure is to many chemicals, fixed-ratio ray designs can be used to assess risk to single chemicals and to specified mixtures of chemicals. This article describes the inference resulting from use of a threshold model for correlated binary data supported by a ray design. An example of the effect of three hepatotoxins in the development of rats is provided. In addition, a two-stage simultaneous optimal design criterion is described for the threshold model along rays of fixed ratios. The approach is illustrated through a simulation study of the hepatotoxin data.

Consequently, Gennings et al. (1998) teaches usage of mixtures and analysis (using fixed ratio rays) of mixture data in rats (test subjects).

The first step of instant claim 6 recites fitting a polynomial additivity to dose-response data. Gennings et al. (1998) teaches the use of an additivity model in section 2.2 on page 4, entitled, "Estimation of an additivity threshold surface." The first equation in section 2.2 of Gennings et al. (1998) teaches such an additivity model quantitatively. Furthermore, the equation on page 1 of Gennings et al. (1998) illustrates such a polynomial to be used to determine additivity in dose response data. As there are three agents interacting in this specific case of Gennings et al. (1998), the highest order term that is not zero is a cubic term, indicating three components (i.e. second step of instant claim 6).

The third and fourth steps of instant claim 6 recite removing a subset of agents from the group or mixture and repeating this step for multiple subsets, respectively. The fifth step of instant claim 6 recites determining the interaction of agents by utilizing the statistical methods based on the results of the third and fourth steps of the method. In the example study in section 4 of Gennings et al. (1998) on pages 8-12 of Gennings et al. (1998), Table 4 of Gennings et al. (1998) on page 11 illustrates modeling the interaction of three agents (DEHP, HEPT, and TCE) by removing two of the three agents, and then examining the effects of a mixture on the mixture in Ray 4, which is a 70:1:29 mixture of DEHP, HEPT, and TCE, respectively. Table 3-5 on page 11-12 of Gennings et al. (1998) tabulate a plurality of full-ray groups. Figure 2 on page 10 if

Gennings et al. (1998) is interpreted as a comparison between an additivity model and a mixture model.

However, Gennings et al. (1998) fails to teach that when the subsets of two agents are removed, the remaining agents (plural) must maintain their relative ratios (i.e. third step of instant claim 6).

Gennings et al. (1997) teaches such a phenomenon in their study, entitled "Detection of departures from additivity in mixtures of many chemicals with a threshold model." Specifically, in comparing the plots Figures 1a and 1b on page 200 of Gennings et al. (1997), a subset of chemicals are removed and a subset of chemical remain. As is stated in the Figure caption:

> Figure 1. Three-dimensional representation of a threshold additivity surface between four chemicals over dose ranges of Chemical 1 and Chemical 2 when: (a) Chemical 3 and Chemical 4 are not included in the mixture (= 0) and (b) Chemical 3 = 0.1 and Chemical 4 = 0.1.

Consequently, while in Figure 1B, all of the constituents are in the mixture, in Figure 1A of Gennings et al. (1997), the subset of chemicals 3 and 4 are removed, leaving chemicals 1 and 2.

The purpose of the study of Gennings et al. (1997) is stated in the introduction, which states, "The evaluation of risk associated with mixtures of chemicals is often needed when the number of chemicals in the mixture is large when the concentration of individual chemicals is low."

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the fixed ratio ray optimization study of Gennings et al. (1998) by use of the additivity models of Gennings et al. (1997) because while

Gennings et al. (1998) measures fixed ratio rays in simple ternary systems, Gennings et al. (1997) uses analogous principles with the advantage of investigating additivity in more complex quaternary mixtures.

Claim 7 is dependent from claim 6 with the additional limitation of specifying a plurality of full ray groups. Table 4 of page 11 of Gennings et al. (1998) lists a plurality of full-ray groups.

Claim 8 is dependent from claim 6 with the additional limitation of carrying out the second and third steps of instant claim 6 for the subset of agents. Gennings et al. (1997) carries out such a process in Figure 1. Specifically, in comparing the plots Figures 1a and 1b on page 200 of Gennings et al. (1997), a subset of chemicals are removed and a subset of chemical remain. As is stated in the Figure caption:

> Figure 1. Three-dimensional representation of a threshold additivity surface between four chemicals over dose ranges of Chemical 1 and Chemical 2 when: (a) Chemical 3 and Chemical 4 are not included in the mixture (= 0) and (b) Chemical 3 = 0.1 and Chemical 4 = 0.1.

Consequently, while in Figure 1B, all of the constituents are in the mixture, in Figure 1A of Gennings et al. (1997), the subset of chemicals 3 and 4 are removed, leaving chemicals 1 and 2.

The purpose of the study of Gennings et al. (1997) is stated in the introduction, which states, "The evaluation of risk associated with mixtures of chemicals is often needed when the number of chemicals in the mixture is large when the concentration of individual chemicals is low."

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the fixed ratio ray optimization study of Gennings et al. (1998) by use of the additivity models of Gennings et al. (1997) because while Gennings et al. (1998) measures fixed ratio rays in simple ternary systems, Gennings et al. (1997) uses analogous principles with the advantage of investigating additivity in more complex quaternary mixtures.

Claim 9 is dependent from claim 6 with the additional limitation of single chemical data being linked to a linear term in said polynomial model. The linear term in the equation on page 1 of Gennings et al. (1998) is related to single chemical data.

Claim 10 is dependent from claim 9 wherein the additivity model and mixture models are depicted as curves. Claim 13 is dependent from claim 6 with the additional limitation of generating a graphical representation of said polynomial in total dose. Figure 2 of Gennings (1998) on page 10 illustrates a comparison of additivity (i.e. model predicted) and mixture model (i.e. observed) with the purpose of comparing the two types of statistical analyses.

Claim 11 is dependent from claim 6 wherein the polynomial is embedded in a generalized linear model. Claim 12 is dependent from claim 6 wherein the polynomial is embedded in a generalized nonlinear model. The equation on page 1 of Gennings et al. (1998) illustrates both the linear and nonlinear polynomials, based on the number of

components in the mixture. While a single-component mixture exhibits linear additivity, multi-component mixtures are fit by a nonlinear model.

Claim 15 is dependent from claim 14 with the additional limitation of determining the region of additivity of the agents and a region of interaction of the agents.

The preamble of claim 15 indicates a method of detecting an interaction among agents in a group or mixture using fixed-ratio ray design and determining whether subsets of said agents also interact.

The study of Gennings et al. (1998), entitled, "Combination threshold models with design optimization along fixed-ratio rays," states in the abstract:

> Threshold models are useful in concentration-effect studies to describe regions of exposure that result in background response. These models are parameterized to estimate the background response, the concentration-effect relationship, and the join-point between the two, called the threshold. If the threshold is different than zero, then it can be inferred that exposure to the chemical at regions below the threshold do not increase risk above background. When the exposure is to many chemicals, fixed-ratio ray designs can be used to assess risk to single chemicals and to specified mixtures of chemicals. This article describes the inference resulting from use of a threshold model for correlated binary data supported by a ray design. An example of the effect of three hepatotoxins in the development of rats is provided. In addition, a two-stage simultaneous optimal design criterion is described for the threshold model along rays of fixed ratios. The approach is illustrated through a simulation study of the hepatotoxin data.

Consequently, Gennings et al. (1998) teaches usage of mixtures and analysis (using fixed ratio rays) of mixture data in rats (test subjects).

The first step of instant claim 15 recites determining an additivity model from the agents in the group. Gennings et al. (1998) teaches the use of an additivity model in section 2.2 on page 4, entitled, "Estimation of an additivity threshold surface." The first equation in section 2.2 of Gennings et al. (1998) teaches such an additivity model quantitatively.

The second step of instant claim 15 recites fitting a mixture model in terms of interaction threshold parameters in terms of total dose. The third step of instant claim 15 recites comparing the additivity and mixture models to detect a departure from additivity, a region of additivity, a region of interaction, and a region of coincidence.

A threshold mixture model is taught through section 2 on page 3 of Gennings et al. (1998), entitled, "Threshold model for proportional data," and section 2.1 on pages 3-4 of Gennings et al. (1998), entitled, "Simultaneous estimation along each ray using a threshold model." Section 2.3.2 on pages 5-6 of Gennings et al. (1998), entitled, "Comparison of predicted thresholds along each mixture ray to the location of the threshold under additivity," compares the additive and mixture models by using thresholds.

Claim 17 is dependent from claim 15, with further limiting steps of removing selected subsets and re-determining additivity.

The first and second steps of instant claim 17 recite removing a subset of agents from the group or mixture and repeating this step for multiple subsets, respectively. The third step of instant claim 17 recites determining the interaction of agents by utilizing the statistical methods based on the results of the first and second steps of the method. In the example study in section 4 of Gennings et al. (1998) on pages 8-12 of Gennings et al. (1998), Table 4 of Gennings et al. (1998) on page 11 illustrates modeling the interaction of three agents (DEHP, HEPT, and TCE) by removing two of the three agents, and then examining the effects of a mixture on the mixture in Ray 4, which is a

70:1:29 mixture of DEHP, HEPT, and TCE, respectively. Table 3-5 on page 11-12 of Gennings et al. (1998) tabulate a plurality of full-ray groups. Figure 2 on page 10 if Gennings et al. (1998) is interpreted as a comparison between an additivity model and a mixture model.

However, Gennings et al. (1998) fails to teach that when the subsets of two agents are removed, the remaining agents (plural) must maintain their relative ratios (i.e. first step of instant claim 1).

Gennings et al. (1997) teaches such a phenomenon in their study, entitled "Detection of departures from additivity in mixtures of many chemicals with a threshold model." Specifically, in comparing the plots Figures 1a and 1b on page 200 of Gennings et al. (1997), a subset of chemicals are removed and a subset of chemical remain. As is stated in the Figure caption:

> Figure 1. Three-dimensional representation of a threshold additivity surface between four chemicals over dose ranges of Chemical 1 and Chemical 2 when: (a) Chemical 3 and Chemical 4 are not included in the mixture (= 0) and (b) Chemical 3 = 0.1 and Chemical 4 = 0.1.

Consequently, while in Figure 1B, all of the constituents are in the mixture, in Figure 1A of Gennings et al. (1997), the subset of chemicals 3 and 4 are removed, leaving chemicals 1 and 2.

The purpose of the study of Gennings et al. (1997) is stated in the introduction, which states, "The evaluation of risk associated with mixtures of chemicals is often needed when the number of chemicals in the mixture is large when the concentration of individual chemicals is low."

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the fixed ratio ray optimization study of Gennings et al. (1998) by use of the additivity models of Gennings et al. (1997) because while Gennings et al. (1998) measures fixed ratio rays in simple ternary systems, Gennings et al. (1997) uses analogous principles with the advantage of investigating additivity in more complex quaternary mixtures.

Claim 16 is dependent from claim 15 with the further limitation of being applicable to a plurality of full-ray groups. Table 4 of page 11 of Gennings et al. (1998) lists a plurality of full-ray groups.

Claim 18 is dependent from claim 14 by carrying Gennings et al. (1997) out such a process of eliminating a subset of agents. Specifically, in comparing the plots Figures 1a and 1b on page 200 of Gennings et al. (1997), a subset of chemicals are removed and a subset of chemical remain. As is stated in the Figure caption:

> Figure 1. Three-dimensional representation of a threshold additivity surface between four chemicals over dose ranges of Chemical 1 and Chemical 2 when: (a) Chemical 3 and Chemical 4 are not included in the mixture (= 0) and (b) Chemical 3 = 0.1 and Chemical 4 = 0.1.

Consequently, while in Figure 1B, all of the constituents are in the mixture, in Figure 1A of Gennings et al. (1997), the subset of chemicals 3 and 4 are removed, leaving chemicals 1 and 2.

The purpose of the study of Gennings et al. (1997) is stated in the introduction, which states, "The evaluation of risk associated with mixtures of chemicals is often

needed when the number of chemicals in the mixture is large when the concentration of individual chemicals is low."

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the fixed ratio ray optimization study of Gennings et al. (1998) by use of the additivity models of Gennings et al. (1997) because while Gennings et al. (1998) measures fixed ratio rays in simple ternary systems, Gennings et al. (1997) uses analogous principles with the advantage of investigating additivity in more complex quaternary mixtures.

Claim 19 is dependent from claim 14 and recites a method of detecting interactions among agents in a group or mixture comprising three steps of determining an additivity model, an interaction threshold model, and statistically comparing both models.

The first step of instant claim 19 recites fitting a polynomial additivity to dose-response data. Gennings et al. (1998) teaches the use of an additivity model in section 2.2 on page 4, entitled, "Estimation of an additivity threshold surface." The first equation in section 2.2 of Gennings et al. (1998) teaches such an additivity model quantitatively. Furthermore, the equation on page 1 of Gennings et al. (1998) illustrates such a polynomial to be used to determine additivity in dose response data. As there are three agents interacting in this specific case of Gennings et al. (1998), the highest order term that is not zero is a cubic term, indicating three components (i.e. second step of instant claim 19).

The third step of instant claim 15 recites comparing the additivity and mixture models to detect a departure from additivity, a region of additivity, a region of interaction, and a region of coincidence.

A threshold mixture model is taught through section 2 on page 3 of Gennings et al. (1998), entitled, "Threshold model for proportional data," and section 2.1 on pages 3-4 of Gennings et al. (1998), entitled, "Simultaneous estimation along each ray using a threshold model." Section 2.3.2 on pages 5-6 of Gennings et al. (1998), entitled, "Comparison of predicted thresholds along each mixture ray to the location of the threshold under additivity," compares the additive and mixture models by using thresholds.

Claim 21 is dependent from claim 19, with further limiting steps of removing selected subsets and re-determining additivity. .

The first and second steps of instant claim 21 recite removing a subset of agents from the group or mixture and repeating this step for multiple subsets, respectively. The third step of instant claim 21 recites determining the interaction of agents by utilizing the statistical methods based on the results of the first and second steps of the method. In the example study in section 4 of Gennings et al. (1998) on pages 8-12 of Gennings et al. (1998), Table 4 of Gennings et al. (1998) on page 11 illustrates modeling the interaction of three agents (DEHP, HEPT, and TCE) by removing two of the three agents, and then examining the effects of a mixture on the mixture in Ray 4, which is a 70:1:29 mixture of DEHP, HEPT, and TCE, respectively. Table 3-5 on page 11-12 of

Gennings et al. (1998) tabulate a plurality of full-ray groups. Figure 2 on page 10 if Gennings et al. (1998) is interpreted as a comparison between an additivity model and a mixture model.

However, Gennings et al. (1998) fails to teach that when the subsets of two agents are removed, the remaining agents (plural) must maintain their relative ratios (i.e. first step of instant claim 1).

Gennings et al. (1997) teaches such a phenomenon in their study, entitled "Detection of departures from additivity in mixtures of many chemicals with a threshold model." Specifically, in comparing the plots Figures 1a and 1b on page 200 of Gennings et al. (1997), a subset of chemicals are removed and a subset of chemical remain. As is stated in the Figure caption:

> Figure 1. Three-dimensional representation of a threshold additivity surface between four chemicals over dose ranges of Chemical 1 and Chemical 2 when: (a) Chemical 3 and Chemical 4 are not included in the mixture (= 0) and (b) Chemical 3 = 0.1 and Chemical 4 = 0.1.

Consequently, while in Figure 1B, all of the constituents are in the mixture, in Figure 1A of Gennings et al. (1997), the subset of chemicals 3 and 4 are removed, leaving chemicals 1 and 2.

The purpose of the study of Gennings et al. (1997) is stated in the introduction, which states, "The evaluation of risk associated with mixtures of chemicals is often needed when the number of chemicals in the mixture is large when the concentration of individual chemicals is low."

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the fixed ratio ray optimization study of Gennings et al.

(1998) by use of the additivity models of Gennings et al. (1997) because while Gennings et al. (1998) measures fixed ratio rays in simple ternary systems, Gennings et al. (1997) uses analogous principles with the advantage of investigating additivity in more complex quaternary mixtures.

Claim 20 is dependent from claim 19 with the further limitation of being applicable to a plurality of full-ray groups. Table 4 of page 11 of Gennings et al. (1998) lists a plurality of full-ray groups.

Claim 22 is dependent from claim 19 by carrying Gennings et al. (1997) out such a process of eliminating a subset of agents. Specifically, in comparing the plots Figures 1a and 1b on page 200 of Gennings et al. (1997), a subset of chemicals are removed and a subset of chemical remain. As is stated in the Figure caption:

> Figure 1. Three-dimensional representation of a threshold additivity surface between four chemicals over dose ranges of Chemical 1 and Chemical 2 when: (a) Chemical 3 and Chemical 4 are not included in the mixture (= 0) and (b) Chemical 3 = 0.1 and Chemical 4 = 0.1.

Consequently, while in Figure 1B, all of the constituents are in the mixture, in Figure 1A of Gennings et al. (1997), the subset of chemicals 3 and 4 are removed, leaving chemicals 1 and 2.

The purpose of the study of Gennings et al. (1997) is stated in the introduction, which states, "The evaluation of risk associated with mixtures of chemicals is often needed when the number of chemicals in the mixture is large when the concentration of individual chemicals is low."

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the fixed ratio ray optimization study of Gennings et al. (1998) by use of the additivity models of Gennings et al. (1997) because while Gennings et al. (1998) measures fixed ratio rays in simple ternary systems, Gennings et al. (1997) uses analogous principles with the advantage of investigating additivity in more complex quaternary mixtures.

Claim 23 is dependent from claim 14 and recites a method of detecting interactions among agents in a group or mixture comprising two steps of fitting a polynomial interaction threshold model and statistically testing different parameters in the polynomial.

The study of Gennings et al. (1998), entitled, "Combination threshold models with design optimization along fixed-ratio rays," states in the abstract:

> Threshold models are useful in concentration-effect studies to describe regions of exposure that result in background response. These models are parameterized to estimate the background response, the concentration-effect relationship, and the join-point between the two, called the threshold. If the threshold is different than zero, then it can be inferred that exposure to the chemical at regions below the threshold do not increase risk above background. When the exposure is to many chemicals, fixed-ratio ray designs can be used to assess risk to single chemicals and to specified mixtures of chemicals. This article describes the inference resulting from use of a threshold model for correlated binary data supported by a ray design. An example of the effect of three hepatotoxins in the development of rats is provided. In addition, a two-stage simultaneous optimal design criterion is described for the threshold model along rays of fixed ratios. The approach is illustrated through a simulation study of the hepatotoxin data.

Consequently, Gennings et al. (1998) teaches usage of mixtures and analysis (using fixed ratio rays) of mixture data in rats (test subjects).

The first step of instant claim 23 recites fitting a polynomial additivity to dose-response data. Gennings et al. (1998) teaches the use of an additivity model in section

2.2 on page 4, entitled, "Estimation of an additivity threshold surface." The first equation in section 2.2 of Gennings et al. (1998) teaches such an additivity model quantitatively. Furthermore, the equation on page 1 of Gennings et al. (1998) illustrates such a polynomial to be used to determine additivity in dose response data. As there are three agents interacting in this specific case of Gennings et al. (1998), the highest order term that is not zero is a cubic term, indicating three components (i.e. second step of instant claim 6).

Claim 24 is dependent from claim 23 with the further limitation of being applicable to a plurality of full-ray groups. Table 4 of page 11 of Gennings et al. (1998) lists a plurality of full-ray groups.

Claim 25 is dependent from claim 23, further comprising additional steps of removing selected subsets and re-determining additivity.

The first and second steps of instant claim 25 recite removing a subset of agents from the group or mixture and repeating this step for multiple subsets, respectively. The third step of instant claim 1 recites determining the interaction of agents by utilizing the statistical methods based on the results of the third and fourth steps of the method. In the example study in section 4 of Gennings et al. (1998) on pages 8-12 of Gennings et al. (1998), Table 4 of Gennings et al. (1998) on page 11 illustrates modeling the interaction of three agents (DEHP, HEPT, and TCE) by removing two of the three agents, and then examining the effects of a mixture on the mixture in Ray 4, which is a

70:1:29 mixture of DEHP, HEPT, and TCE, respectively. Table 3-5 on page 11-12 of Gennings et al. (1998) tabulate a plurality of full-ray groups. Figure 2 on page 10 if Gennings et al. (1998) is interpreted as a comparison between an additivity model and a mixture model.

However, Gennings et al. (1998) fails to teach that when the subsets of two agents are removed, the remaining agents (plural) must maintain their relative ratios (i.e. third step of instant claim 6).

Gennings et al. (1997) teaches such a phenomenon in their study, entitled "Detection of departures from additivity in mixtures of many chemicals with a threshold model." Specifically, in comparing the plots Figures 1a and 1b on page 200 of Gennings et al. (1997), a subset of chemicals are removed and a subset of chemical remain. As is stated in the Figure caption:

> Figure 1. Three-dimensional representation of a threshold additivity surface between four chemicals over dose ranges of Chemical 1 and Chemical 2 when: (a) Chemical 3 and Chemical 4 are not included in the mixture (= 0) and (b) Chemical 3 = 0.1 and Chemical 4 = 0.1.

Consequently, while in Figure 1B, all of the constituents are in the mixture, in Figure 1A of Gennings et al. (1997), the subset of chemicals 3 and 4 are removed, leaving chemicals 1 and 2.

The purpose of the study of Gennings et al. (1997) is stated in the introduction, which states, "The evaluation of risk associated with mixtures of chemicals is often needed when the number of chemicals in the mixture is large when the concentration of individual chemicals is low."

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the fixed ratio ray optimization study of Gennings et al. (1998) by use of the additivity models of Gennings et al. (1997) because while Gennings et al. (1998) measures fixed ratio rays in simple ternary systems, Gennings et al. (1997) uses analogous principles with the advantage of investigating additivity in more complex quaternary mixtures.

Claim 26 is dependent from claim 23 with the additional limitation of having single chemical data wherein the single chemical data is obtained in test subjects.

The study of Gennings et al. (1998), entitled, "Combination threshold models with design optimization along fixed-ratio rays," states in the abstract:

> Threshold models are useful in concentration-effect studies to describe regions of exposure that result in background response. These models are parameterized to estimate the background response, the concentration-effect relationship, and the join-point between the two, called the threshold. If the threshold is different than zero, then it can be inferred that exposure to the chemical at regions below the threshold do not increase risk above background. When the exposure is to many chemicals, fixed-ratio ray designs can be used to assess risk to single chemicals and to specified mixtures of chemicals. This article describes the inference resulting from use of a threshold model for correlated binary data supported by a ray design. An example of the effect of three hepatotoxins in the development of rats is provided. In addition, a two-stage simultaneous optimal design criterion is described for the threshold model along rays of fixed ratios. The approach is illustrated through a simulation study of the hepatotoxin data.

Consequently, Gennings et al. (1998) teaches usage of mixtures and analysis (using fixed ratio rays) of mixture data in rats (test subjects).

Claim 30 is drawn to software for detecting interactions among agents in a group or mixture comprising seven steps.

The preamble of claim 30 indicated software for detecting an interaction among agents in a group or mixture using fixed-ratio ray design and determining whether subsets of said agents also interact. The first step of instant claim 30 recites determining an additivity model from single dose-response data. The second step of instant claim 30 recites fitting a mixture model in terms of total dose to mixture-dose response data from fixed-ratio rays for said agents in said group or mixture. The third step of instant claim 30 recites comparing the additivity and mixture models. The fourth and fifth steps of instant claim 30 recite removing a subset of agents from the group or mixture and repeating this step for multiple subsets, respectively. The sixth step of instant claim 30 recites determining the interaction of agents by utilizing the statistical methods based on the results of the fourth and fifth steps of the method. The seventh step of claim 30 provides the results in the form of a plot or table.

The study of Gennings et al. (1998), entitled, "Combination threshold models with design optimization along fixed-ratio rays," states in the abstract:

> Threshold models are useful in concentration-effect studies to describe regions of exposure that result in background response. These models are parameterized to estimate the background response, the concentration-effect relationship, and the join-point between the two, called the threshold. If the threshold is different than zero, then it can be inferred that exposure to the chemical at regions below the threshold do not increase risk above background. When the exposure is to many chemicals, fixed-ratio ray designs can be used to assess risk to single chemicals and to specified mixtures of chemicals. This article describes the inference resulting from use of a threshold model for correlated binary data supported by a ray design. An example of the effect of three hepatotoxins in the development of rats is provided. In addition, a two-stage simultaneous optimal design criterion is described for the threshold model along rays of fixed ratios. The approach is illustrated through a simulation study of the hepatotoxin data.

Consequently, Gennings et al. (1998) teaches usage of mixtures and analysis (using fixed ratio rays) of mixture data in rats (test subjects).

The first step of instant claim 30 recites determining an additivity model from single dose-response data. Gennings et al. (1998) teaches the use of an additivity model in section 2.2 on page 4, entitled, "Estimation of an additivity threshold surface." The first equation in section 2.2 of Gennings et al. (1998) teaches such an additivity model quantitatively.

The second step of instant claim 30 recites fitting a mixture model in terms of total dose to mixture-dose response data from fixed-ratio rays for said agents in said group or mixture. The third step of instant claim 30 recites comparing the additivity and mixture models. A threshold mixture model is taught through section 2 on page 3 of Gennings et al. (1998), entitled, "Threshold model for proportional data," and section 2.1 on pages 3-4 of Gennings et al. (1998), entitled, "Simultaneous estimation along each ray using a threshold model." Section 2.3.2 on pages 5-6 of Gennings et al. (1998), entitled, "Comparison of predicted thresholds along each mixture ray to the location of the threshold under additivity," compares the additive and mixture models by using thresholds.

The fourth and fifth steps of instant claim 30 recite removing a subset of agents from the group or mixture and repeating this step for multiple subsets, respectively. The sixth step of instant claim 30 recites determining the interaction of agents by utilizing the statistical methods based on the results of the fourth and fifth steps of the method. In the example study in section 4 of Gennings et al. (1998) on pages 8-12 of Gennings et al. (1998), Table 4 of Gennings et al. (1998) on page 11 illustrates modeling the interaction of three agents (DEHP, HEPT, and TCE) by removing two of the three

agents, and then examining the effects of a mixture on the mixture in Ray 4, which is a 70:1:29 mixture of DEHP, HEPT, and TCE, respectively. Table 3-5 on page 11-12 of Gennings et al. (1998) tabulate a plurality of full-ray groups. Figure 2 on page 10 if Gennings et al. (1998) is interpreted as a comparison between an additivity model and a mixture model.

However, when Gennings et al. (1998) fails to teach that when the subsets of two agents are removed, the remaining agents (plural) must maintain their relative ratios (i.e. fourth step of instant claim 30).

Gennings et al. (1997) teaches such a phenomenon in their study, entitled "Detection of departures from additivity in mixtures of many chemicals with a threshold model." Specifically, in comparing the plots Figures 1a and 1b on page 200 of Gennings et al. (1997), a subset of chemicals are removed and a subset of chemical remain. As is stated in the Figure caption:

> Figure 1. Three-dimensional representation of a threshold additivity surface between four chemicals over dose ranges of Chemical 1 and Chemical 2 when: (a) Chemical 3 and Chemical 4 are not included in the mixture (= 0) and (b) Chemical 3 = 0.1 and Chemical 4 = 0.1.

Consequently, while in Figure 1B, all of the constituents are in the mixture, in Figure 1A of Gennings et al. (1997), the subset of chemicals 3 and 4 are removed, leaving chemicals 1 and 2.

The purpose of the study of Gennings et al. (1997) is stated in the introduction, which states, "The evaluation of risk associated with mixtures of chemicals is often needed when the number of chemicals in the mixture is large when the concentration of individual chemicals is low."

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the fixed ratio ray optimization study of Gennings et al. (1998) by use of the additivity models of Gennings et al. (1997) because while Gennings et al. (1998) measures fixed ratio rays in simple ternary systems, Gennings et al. (1997) uses analogous principles with the advantage of investigating additivity in more complex quaternary mixtures.

It would have been obvious to automate this process of Gennings et al (1998) in view of Gennings et al. (1997) on a computer for more expeditious and accurate results. As stated in MPEP section 2144.04:

> In re Venner, 262 F.2d 91, 95, 120 USPQ 193, 194 (CCPA 1958) (Appellant argued that claims to a permanent mold casting apparatus for molding trunk pistons were allowable over the prior art because the claimed invention combined "old permanent-mold structures together with a timer and solenoid which automatically actuates the known pressure valve system to release the inner core after a predetermined time has elapsed." The court held that broadly providing an automatic or mechanical means to replace a manual activity which accomplished the same result is not sufficient to distinguish over the prior art.).

Thus, automation of the procedure of both Gennings et al. articles as instantly claimed is not sufficient to distinguish this procedure over both Gennings et al. articles.

Claim 31 is drawn to software for detecting interactions among agents in a group or mixture comprising six steps.

The preamble of claim 31 indicates software for detecting an interaction among agents in a group or mixture using fixed-ratio ray design and determining whether subsets of said agents also interact. The first step of instant claim 31 recites fitting a polynomial additivity to dose-response data. The second step of instant claim 31 is

statistical analysis of higher order terms in the polynomial model. The third and fourth steps of instant claim 31 recite removing a subset of agents from the group or mixture and repeating this step for multiple subsets, respectively. The fifth step of instant claim 31 recites determining the interaction of agents by utilizing the statistical methods based on the results of the third and fourth steps of the method. The sixth step of claim 31 provides the results in the form of a plot or table.

The study of Gennings et al. (1998), entitled, "Combination threshold models with design optimization along fixed-ratio rays," states in the abstract:

> Threshold models are useful in concentration-effect studies to describe regions of exposure that result in background response. These models are parameterized to estimate the background response, the concentration-effect relationship, and the join-point between the two, called the threshold. If the threshold is different than zero, then it can be inferred that exposure to the chemical at regions below the threshold do not increase risk above background. When the exposure is to many chemicals, fixed-ratio ray designs can be used to assess risk to single chemicals and to specified mixtures of chemicals. This article describes the inference resulting from use of a threshold model for correlated binary data supported by a ray design. An example of the effect of three hepatotoxins in the development of rats is provided. In addition, a two-stage simultaneous optimal design criterion is described for the threshold model along rays of fixed ratios. The approach is illustrated through a simulation study of the hepatotoxin data.

Consequently, Gennings et al. (1998) teaches usage of mixtures and analysis (using fixed ratio rays) of mixture data in rats (test subjects).

The first step of instant claim 31 recites fitting a polynomial additivity to dose-response data. Gennings et al. (1998) teaches the use of an additivity model in section 2.2 on page 4, entitled, "Estimation of an additivity threshold surface." The first equation in section 2.2 of Gennings et al. (1998) teaches such an additivity model quantitatively. Furthermore, the equation on page 1 of Gennings et al. (1998) illustrates such a polynomial to be used to determine additivity in dose response data. As there are three agents interacting in this specific case of Gennings et al. (1998), the highest order term

that is not zero is a cubic term, indicating three components (i.e. second step of instant claim).

The third and fourth steps of instant claim 31 recite removing a subset of agents from the group or mixture and repeating this step for multiple subsets, respectively. The fifth step of instant claim 31 recites determining the interaction of agents by utilizing the statistical methods based on the results of the third and fourth steps of the method. In the example study in section 4 of Gennings et al. (1998) on pages 8-12 of Gennings et al. (1998), Table 4 of Gennings et al. (1998) on page 11 illustrates modeling the interaction of three agents (DEHP, HEPT, and TCE) by removing two of the three agents, and then examining the effects of a mixture on the mixture in Ray 4, which is a 70:1:29 mixture of DEHP, HEPT, and TCE, respectively. Table 3-5 on page 11-12 of Gennings et al. (1998) tabulate a plurality of full-ray groups. Figure 2 on page 10 if Gennings et al. (1998) is interpreted as a comparison between an additivity model and a mixture model.

However, Gennings et al. (1998) fails to teach that when the subsets of two agents are removed, the remaining agents (plural) must maintain their relative ratios (i.e. third step of instant claim 6).

Gennings et al. (1997) teaches such a phenomenon in their study, entitled "Detection of departures from additivity in mixtures of many chemicals with a threshold model." Specifically, in comparing the plots Figures 1a and 1b on page 200 of Gennings et al. (1997), a subset of chemicals are removed and a subset of chemical remain. As is stated in the Figure caption:

Figure 1. Three-dimensional representation of a threshold additivity surface between four chemicals over dose ranges of Chemical 1 and Chemical 2 when: (a) Chemical 3 and Chemical 4 are not included in the mixture (= 0) and (b) Chemical 3 = 0.1 and Chemical 4 = 0.1.

Consequently, while in Figure 1B, all of the constituents are in the mixture, in Figure 1A of Gennings et al. (1997), the subset of chemicals 3 and 4 are removed, leaving chemicals 1 and 2.

The purpose of the study of Gennings et al. (1997) is stated in the introduction, which states, "The evaluation of risk associated with mixtures of chemicals is often needed when the number of chemicals in the mixture is large when the concentration of individual chemicals is low."

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the fixed ratio ray optimization study of Gennings et al. (1998) by use of the additivity models of Gennings et al. (1997) because while Gennings et al. (1998) measures fixed ratio rays in simple ternary systems, Gennings et al. (1997) uses analogous principles with the advantage of investigating additivity in more complex quaternary mixtures.

It would have been obvious to automate this process of Gennings et al (1998) in view of Gennings et al. (1997) on a computer for more expeditious and accurate results. As stated in MPEP section 2144.04:

> In re Venner, 262 F.2d 91, 95, 120 USPQ 193, 194 (CCPA 1958) (Appellant argued that claims to a permanent mold casting apparatus for molding trunk pistons were allowable over the prior art because the claimed invention combined "old permanent-mold structures together with a timer and solenoid which automatically actuates the known pressure valve system to release the inner core after a predetermined time has elapsed." The court held that broadly providing an automatic or mechanical means to replace a manual activity which accomplished the same result is not sufficient to distinguish over the prior art.).

Thus, automation of the procedure of both Gennings et al. articles as instantly claimed is not sufficient to distinguish this procedure over both Gennings et al. articles.

Response to Arguments

Applicant's arguments filed 27 April 2007 have been fully considered and they are persuasive. New grounds of rejection are applied.

Conclusion

No claim is allowed.

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the central PTO Fax Center. The faxing of such pages must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CFR § 1.6(d)). The Central PTO Fax Center Number is (571) 273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Russell Negin, Ph.D., whose telephone number is (571) 272-1083. The examiner can normally be reached on Monday-Friday from 7am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's Supervisor, Ram Shukla, Supervisory Patent Examiner, can be reached at (571) 272-0735.

Information regarding the status of the application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information on the PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

RSN
28 May 2007

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SUPERVISORY PATENT EXAMINER